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The main objectives of Phase I have been attained. Detailed, prospective, multidisciplinary neurobehavioral evaluations are ongoing in 72 HIV+, largely asymptomatic patients; plus 62 normal, depressed, or neurologic diseased controls. We have shown variable abnormalities in EEG, EPs, & MRI, as well as more consistent abnormalities in CSF & specific cognitive tasks of attention & information processing. This latter occurs in a subgroup of HIV+ patients, but not in depressed controls, & is associated with otherwise normal performance on standard tests of intelligence, language, & memory. Performance on reaction time tasks has been shown to deteriorate over time & is highly correlated with changes in CSF quinolinic acid, an excitatory neurotoxin. However, it must be emphasized that the presence of these abnormalities, per se, cannot at present be translated into an indication of impaired job performance. Phase II studies will establish the incidence of information processing disorders in HIV+ patients by using a briefer but more focused battery in a larger & less biased population. A brief neurobehavioral screening battery has been developed & successfully tested for use in therapeutic trials. In collaboration with the Department of Psychiatry, we will also explore the interaction between these findings & psychiatric & psychosocial variables. MRI, CSF, EEG, & other CNS biologic abnormalities uncovered in Phase I, will be pursued in the original patients as well as in a subgroup of new patients, including more advanced patients with AIDS.

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APPENDIX C

FOREWORD

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TABLE OF CONTENTS

NEUROBEHAVIORAL CONSEQUENCES OF HTLV-III BRAIN INFECTION AND ACQUIRED IMMUNE DEFICIENCY SYNDROME (AIDS) ENCEPHALOPATHY: A PROSPECTIVE STUDY

ANNUAL REPORT (87PP7856)

INTRODUCTION

The invasion of the central nervous system by the virus in the earliest stages of HIV-1 infection has now been well established, and the clinical syndromes associated with advanced disease, including the AIDS-Dementia syndrome, have been described. The clinical consequences of this CNS invasion in patients who are not significantly immunocompromised (WR stage 1-3), however, remains a subject of continued debate. This is especially so with regard to possible cognitive and attentional changes in early HIV infection. Igor Grant and colleagues in San Diego have reported an increased incidence of neuropsychological abnormalities in otherwise asymptomatic HIV seropositive patients, while the MACS, and CDC studies have failed to confirm this.[1,2,3,4] The implications of this controversy can be far reaching, since they open the possibility that HIV infection alone could be sufficient to impair job performance in certain critical occupations.

The primary objectives of Phase I of the present study are to:

1. Prospectively characterize the neurological and cognitive manifestations of early HIV infection.

2. To develop a screening instrument to detect the early onset of neurobehavioral changes in HIV infection.

3. To investigate host, virus, infection, and epidemiologic factors affecting these manifestations and their progression.

4. To establish a structure for the systematic testing and evaluation of patients in drug trials.

BODY

These objectives have been addressed by establishing a cohort of HIV infected patients who have been prospectively followed with detailed multidisciplinary evaluations every six months for up to two years. Each evaluation includes comprehensive neurological examination, neuropsychological testing, psychiatric examination, lumbar puncture, magnetic resonance imaging (MRI), EEG, Evoked Potentials (EP), and Brain Electrical Activity Mapping (BEAM).

Specialized laboratory studies completed include blood and spinal fluid (CSF) HIV cultures, CSF quinolinate and kynurinate, and assay for a GP120-like neurotoxin. A frozen serum, CSF, and cell bank is maintained for additional experimental studies currently under negotiation.

RESULTS

The first objective has been largely attained. To date 134 individuals have been enrolled in the study; this includes 72 HIV+ individuals; 29 HIV seronegative normal controls, 23 HIV- controls with adjustment disorder or depression; and 19 HIV negative controls with other neurologic disease. Of the HIV positive subjects, 56 have been evaluated twice (six months), 41 have been evaluated three times (0, 6, and 12 months), and 18 have been seen four times (0, 6, 12, and 18 months). On study entry, 57% were in WR stage 1-2, 21% in WR 3-4, and 21% in WR 5-6.

The standard neurologic examination remained essentially normal in the majority of patients over a 12-month period. Aside from occasional sensory symptoms, no systematic pattern of deterioration was found. CSF was initially abnormal in up to 98% of patients and remained so in follow-up examinations. Positive CSF HIV cultures have correlated with elevated CSF IgG and with elevated cell counts. Hyperintense lesions were seen on MRI initially in 31%; new lesions developed in an additional 20% at 12 months. Only one EEG was initially abnormal, but an additional 20% became abnormally slow at 12 months. Somatosensory EPs were abnormal in 11%, but visual and auditory EP remained normal in most. In our population, there were no strong correlations between WR stage of illness and any of the above findings.

As initialiy hypothesized, the neuropsychological evaluation of these patients has been the most revealing. Ongoing analyses have shown a subtle cognitive dysfunction in a subgroup of the HIV infected patients that is not attributable to current degree of depression or anxiety, and is not seen in depressed HIV-negative controls or even in otherwise neurologically impaired patients with multiple sclerosis. These changes are consistent with an early "subcortical dementia" with slowed information processing as a prominent feature. Importantly, progressive deterioration of performance on reaction time tasks and in decision time has been documented on repeated evaluation over 12 months. These abnormalities are not correlated to WR stage of illness, or to presence of symptoms. On the other hand, these same patients perform generally within normal limits on a standard battery of neuropsychological tests assessing overall intelligence, language, and memory function. It is important to note that our findings on these latter tests do not disagree with those of the MACS and CDC studies. Significantly, however, the neuropsychological batteries used in those studies did not include reaction time tasks sensitive to a "subcortical dementia". Results of smaller studies by other investigators who have included such tasks tend to agree with our findings.

With regard to objective 2, the detailed examinations described above have allowed us to reduce the neurologic and neuropsychologic batteries considerably for Phase II of the project, in which a larger, and less biased sample of patients will be evaluated at 12-month intervals in order to address the true incidence of information processing abnormalities in early HIV infection. While the new battery is still more comprehensive than a simple screen, it can be completed in about one hour.

Objective 3, the biology of CNS HIV infection, is still under active investigation. Perhaps our most exciting finding to date has been the high correlation between progressive slowing in reaction time tasks and a rise in the levels of CSF quinolinic acid (QUIN) over six months ($r=.85$, $p<.01$). QUIN is an endogenous excitatory neurotoxin which acts specifically at the NMDA glutamate receptors; it will reproduce the pathology of the subcortical dementia of Huntington's disease when administered to mice. QUIN is a metabolite of tryptophan in a reaction catalyzed by indoleamine-2,3 dioxygenase, an enzyme which is induced by interferon. In collaboration with Dr. Melvin Heyes of the NIMH and Dr. R. Price and B. Brew of Cornell, we have demonstrated abnormally elevated QUIN in our early HIV infected patients as well as in more advanced patients, sometimes to a marked degree. In contrast, QUIN levels are normal in other neurologic diseases, including various dementias. QUIN levels are correlated with serum B_2 microglobulin (a marker of interferon activity) and with serum neopterin (a marker of macrophage activation), suggesting that the elevated serum interferon in HIV infection is responsible for the chronic QUIN elevations. This is further supported by the finding that treatment with AZT will decrease CSF QUIN levels, as well as B_2 microglobulin; and will improve mental function, at least temporarily. Our findings correlating QUIN elevations to slowed information processing thus suggest one possible metabolic explanation for some of the mental changes seen in advanced AIDS. Further studies will continue to investigate these findings, as well as possible correlations of QUIN with other lymphokines, and changes in quinolinate in response to various therapies. A small clinical trial of an NMDA receptor antagonist in seropositive patients with slowed information processing would

solidify the possible role of an excitotoxin in producing this mental change, and is now being considered.

We have pursued another possible link to biological changes in collaboration with Drs. Douglas Brennerman and Candace Pert of the NIH. In preliminary studies we have found that CSF from 9/18 of our early HIV patients will induce neuronal killing *in vitro* at a 1:100,000 dilution; this effect is prevented by Peptide-T. Only one multiple sclerosis case out of 10 HIV seronegative controls showed similar findings. VIP neuropeptide and a monoclonal antibody against mouse CD4 will also reverse this neuronal killing, suggesting that it represents a GP-120 associated neurotoxicity. However, we have not yet found any significant correlations between these CSF findings and clinical change.

We are now pursuing another avenue of investigation in collaboration with Dr. Michael Oldstone of the Scripps Clinic in La Jolla, who has found an unusual 43 KD astrocyte protein which cross reacts with an immunodominant epitope of GP-120 in AIDS patients. He will analyze CSF and serum from our patients in hopes of finding another possible correlate to neurologic or cognitive changes.

Objective 4, the potential role of these neurologic or neuropsychological changes as clinical markers of change in therapeutic trials has also been addressed. Brief serial neurologic and neuropsychologic evaluations were performed as a part of a pilot trial of Poly-ICLC in eight patients with advanced disease (RV-14). While no conclusions as to efficacy can be drawn at this time, we have shown a possible stabilization of performance on certain tasks which would be expected to deteriorate over six months based on findings in our larger, untreated group. In particular, performance on the reaction time and Purdue pegboard tasks appears to improve while patients were on drugs, and deteriorate when dosage is reduced. These findings support our hypothesis that specific, well targeted neuropsychological testing can be of value as an outcome criterion in therapeutic trials. In fact, it may represent the only purely clinical performance variable available for studies in otherwise asymptomatic seropositive patients.

CONCLUSIONS

A total of 32 publications/presentations have resulted from the project to date.

The principal objectives of Phase I of the project have now been attained. Detailed, prospective, multidisciplinary neurobehavioral evaluations are ongoing in 72 seropositive, largely asymptomatic patients; plus 62 normal, depressed, or neurologic diseased seronegative controls. We have shown variable abnormalities in EEG, EPs, and MRI, as well as more consistent abnormalities in CSF and specific cognitive tasks of attention and information processing. This latter occurs in a subgroup of seropositive patients, but not in depressed controls, and is associated with otherwise normal performance on standard tests of intelligence, language, and memory. Performance on reaction time tasks has been shown to deteriorate over time and is highly correlated with changes in CSF quinolinic acid, an excitatory neurotoxin. However, it must be emphasized that the presence of these abnormalities, per se, cannot at present be translated into an indication of impaired job performance.

Studies now beginning in Phase II of the project will establish the incidence of information processing disorders in HIV seropositive patients by using a briefer but more focused battery in a larger and less biased population. A brief neurobehavioral screening battery has also been developed and successfully tested for use in therapeutic trials. In collaboration with the Department of Psychiatry (protocol RV-26), our group will also explore the interaction between these findings and psychiatric and psychosocial variables. MRI, CSF, electrophysiologic, and other CNS biologic abnormalities uncovered in Phase I, will be pursued in the original patients as well as in a subgroup of new patients, including more advanced patients with AIDS.

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Heyes MP, Brew BJ, Martin A, Price RW, Salazar AM, et al. *CEREBROSPINAL FLUID QUINOLINIC ACID AND KYNURENIC ACID IN HIV-1 INFECTION AND AIDS DEMENTIA COMPLEX: INCREASED RATIO OF QUINOLINIC ACID TO KYNURENIC ACID.* Annals of Neurology. (In Review)

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